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A 6-year analysis of cardiovascular implantable electronic device-related endocarditis

Lead endocarditis

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Abstract
Aim: Advances in interventional cardiology have increased the frequency of use of devices such as cardiovascular implanted electronic devices (CIED) used in cardiac arrhythmias. Endocarditis due to these devices increases morbidity and mortality.
Material and Methods: Demographic data, laboratory tests, results of blood cultures, transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) data of 48 patients who developed infective endocarditis due to CIED in our hospital between January 1, 2013 and March 1, 2019 were retrospectively analyzed.
Results: A total of 48 patients were included in this study. The ratio of females (n=24) and males (n=24) was equal. The mean age of all patients was 55 years. In the surviving patients, in order of frequency of occurrence, hypertension (HT) was in 13 patients (86%), chronic renal failure (CKD) in 9 patients (47%), and diabetes mellitus (DM) in 8 patients (72%). Of the patients who died, 10 (52%) had CRF, 3 (27%) had DM, 2 (66%) had HT and chronic obstructive pulmonary disease (COPD). The most common symptoms in surviving patients were, respectively, fever in 26 (78%), malaise in 19 (76%), respiratory distress in 11 (61%). The most common symptoms in deceased patients were respiratory distress in 7 (%38), fever in 7 (21%), fatigue in 6 (%24); 14 (29%) of the patients referred to our clinic started antibiotic treatment at an external center. Growth was detected in 26 (54%) of all blood cultures. The most frequently isolated pathogens were, respectively, Staphylococcus aureus (n=11) 42%, Streptococcus spp.(n=6) 23%, Enterococcus faecium (n=4) 15%, Citrobacter spp. (n=2) 7%, Diphtheroid spp.(n=1) 3%, Acinetobacter baumannii (n=1) 3%, Brucella mitis (n=1) 3%. Vegetation was observed on the lead in 13 (27%) performed TTEs and/or TEEs. From the time of diagnosis, the average time of surgery was 6 days in surviving patients and 11 days in patients who died.
Discussion: The number of studies and cases related to endocarditis due to CIEDs is limited in our country. Although CIED-related endocarditis is a rare complication of cardiac device implantation, its morbidity and mortality remain high.

Keywords
Lead Endocarditis, Cardiac Implantable Electronic Device, Pacemaker

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Introduction

CIEDs are used in the treatment of symptomatic bradycardia and heart failure in patients at risk of sudden cardiac death due to ventricular arrhythmia.

The total number of CIEDs implanted per 1 000 000 people per year is 247. With the aging of the population, it is predicted that these devices will be implanted more and more in our country, as in the whole world [1]. In our country, a total of 22 732 CIEDs were implanted in 2016, 9993 of which were permanent pacemakers, 3485 cardiac resynchronization therapy devices and 9254 were ICDs (available at: https://www.escardio.org/static_file/Escardio/Subspecialty/ EHRA/Publications/Documents/2017/ehra-white-book-2017.pdf.). The Duke criteria are used in the diagnosis of infective endocarditis (IE) due to CIED, vegetations are seen on device wires, adjacent endocardial surfaces or on the valve, but the presence of vegetation only at the tip of the wire can be considered as IE.

It is difficult to diagnose cardiac device-related IE. If a patient with a cardiac device has an unexplained fever, infective endocarditis should be considered first [2]. CIED-associated infective endocarditis accounts for 10-23% of all CIED-related infections. Among all infective endocarditis cases, the rate of those associated with CIED is 10% both in our country and in the world. Although it is recommended to continue the IV antibiotic treatment for at least 2 weeks after the device removal, if the blood culture positivity continues in the first 24 hours after device removal, this period should be extended to 4 weeks [3-5].

Material and Methods

We retrospectively analyzed 48 patients who were followed up in our hospital with the diagnosis of CIED-related endocarditis between January 1, 2013 and March 1, 2019. Patient demographics, TTE/TEE, laboratory findings, causative pathogens and surgical approaches were examined. Ethical approval numbered 2020-3/03-296 and dated 20.04.2020 was obtained from the Non-Interventional Clinical Research Ethics Committee of the Health Sciences University Kartal Kosuyolu Yuksek Ihtisas Training and Research Hospital.

Statistics

Descriptive statistics (mean, median, standard deviation, etc.) were used while summarizing continuous numerical variables. Two-group comparison of numerical variables was analyzed with the Mann-Whitney U test. The statistical significance limit was taken as $p<0.05$.

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

The ratio of female and male patients was equal, and the mean age was 55±14.6 years. Mortality developed in 3 (17%) female patients and 9 (38%) male patients. The mean age of the patients living with CIED was 53±11.4 years, and the mean age of the patients who died was 64±12.2 years. The median length of hospital stay was 31.5 (29.0-33.0) days in patients who survived, and 29.5 (28.0-33.5) days in patients who died. The most common symptoms in surviving patients were, respectively, fever in 26 (78%), fatigue in 19 (76%) patients, respiratory distress in 11 (61%) patients. Among those who died, respiratory distress was present in 7 (38%), fever in 7 (21%), and fatigue in 6 (24%) patients (Table 1).

HT, COPD, and obesity were found to be statistically significant (p=0.208, 0.150, 0.150). When comorbid factors were taken into account, the underlying disease was significantly higher in those who died (p=0.012). In the surviving patients, in order of frequency of occurrence, hypertension (HT) was in 13 patients (86%), chronic renal failure (CKD) in 9 patients (47%), and diabetes mellitus (DM) in 8 patients (72%). Of the patients who died, 10 (52%) had CRF, 3 (27%) had DM, and 2 (66%) had HT and Chronic Obstructive Pulmonary Disease (COPD) (Table 2).

Of the 48 patients followed up with CIED infection, 14 (29.1%) were referred from external centers. In these patients, antibiotics were started before blood cultures were taken. Growth was detected in the blood cultures of 26 (54%) patients. The isolated pathogens, in order of frequency of occurrence, were Staphylococcus aureus (n=11) 42%, Streptococcus spp. (n=6) 23%, Enterococcus faecium (n=4)1%1, Citrobacter spp. (n=2) 7%, Diphtheroid spp.(n=1) 3%, Acinetobacter baumannii (n=1) 3%, and Brucella mitis (n=1) 3%.

Of the patients who were followed up with CIED, 33 (68%) were patients with natural valves and 15 (31%) were patients with prosthetic valves. Considering the valve involvement of vegetation, 9 (18%) patients had aortic valve involvement, 8 (16%) patients had mitral valves, and 1 (2%) patient had a tricuspid valve. In TEE and/or TTE performed on the patients, vegetation on the lead was detected in 13 (27%) patients. Serum leukocytosis was present in 16 (70%) of the surviving patients and 7 (30%) of the deceased patients ($p = 0.311$). C-reactive protein (CRP) was found to be higher than 20 mg/dl in 27 (80%) of the survivors and in 7 (20%) of the patients who died ($p= 0.019$). There were 9 (19%) patients with a laboratory value of procalcitonin greater than 1 (ng/ml), and 5 (55%) of these patients died.

For various reasons, 25 out of 48 people (52%) received antibiotics before the examples of blood cultures were taken. The start of antibiotic therapy in the preliminary diagnosis of CIED infection was 41 hours in living patients and 9.9 hours in deceased patients. In these patients, one of the problems in the treatment was lead removal, which was removed by two different methods. The CIEDs we applied to 19 patients (39%) in our study were removed percutaneously. Instruments and techniques such as transvenous manual traction, locking stylet, rotational mechanical dilator sheath systems and traps have been used. The surgical method was applied in 29 (60%) patients.

Surgery

The mediastinum was reached by median sternotomy under general anesthesia. The patient was heparinized and, after bicaval cannulation of the aorta, cardiopulmonary bypass (CPB) was initiated. The aorta was cross-clamped and cardiac arrest was achieved with warm blood cardioplegia. Then, the inner surface of the right atrium was reached by right atriotomy, the infected and thrombosed lead was examined and removed from the atrium and ventricular wall with sharp and blunt dissections. If there was an additional cardiac problem, an intervention was performed. A temporary intracardiac pacemaker was implanted

in all patients when exiting CPB. From the time of diagnosis, the average time of surgery was 6 days in surviving patients and 11 days in patients who died.

Table 1. Evaluation of symptoms and findings of patients followed up with CIED infection.

Parameters		Total (n=48)	Alive(%) (n=36)	Deceased (%) (n=12)	P
Age (Mean)		55	52.9	63.8	
Gender	Male	24	15 (%62.5)	9 (%37.5)	0.04
	Female	24	21 (%87.5)	3 (%12.5)	
Fever		33	26 (%78.8)	7 (%21.2)	0.369
Respiratory distress		18	11 (%61.1)	7 (%38.9)	0.085
Fatigue		25	19 (%76.0)	6 (%24.0)	0.869
Clouding of consciousness		7	4 (%57.1)	3 (%42.9)	0.231
Chest pain		5	4 (%80.0)	1 (%20.0)	0.633
Weight loss		5	5 (%100.0)	0 (%0.0)	0.220
Syncope		4	3 (%75.0)	1 (%25.0)	0.743
Palpitation		4	3 (%75.0)	1 (%25.0)	0.743
Nausea		4	3 (%75.0)	1 (%25.0)	0.743
Rash		1	0 (%0.0)	1 (%100.0)	0.250

Table 2. Underlying diseases in patients followed up with CIED infection.

	Total (n=48)	Alive (%) (n=36)	Deceased (%) (n=12)	P
Co-morbid Disease	21	12 (%57.1)	9 (%42.9)	0.012
Chronic Kidney Failure	19	9 (%47.4)	10 (%52.6)	0.000
Hypertension	15	13 (%86.7)	2 (%13.3)	0.208
Diabetes Mellitus	11	8 (%72.7)	3 (%27.3)	0.843
Cerebrovascular event	4	3 (%75.0)	1 (%25.0)	0.743
COPD	3	1 (%33.3)	2 (%66.7)	0.150
Obesity	3	1 (%33.3)	2 (%66.7)	0.150
Malignancy	3	3 (%100.0)	0 (%0.0)	0.413

Table 3. Laboratory findings

		Average	Median	Std. Deviation	Minimum	Maximum	P
Sedimentation (mm/h)	Alive	53,61	56	31,45	5	117	0,581
	Deceased	62,78	51	30,87	23	120	
CRP (mg/L)	Alive	8,22	7,67	6,77	0,09	23	0,019
	Deceased	44,31	16	58,84	2	157	
Leukocytes ($10^3/mm^3$)	Alive	10,38	9,1	4,81	1,9	21,9	0,311
	Deceased	11,15	11	3,44	7,3	20	
Platelets ($10^3/mm^3$)	Alive	253,76	214	134,68	90,4	660	0,312
	Deceased	198,58	197	77,12	112	350	
MPV	Alive	8,7	8,25	1,47	6,1	12,7	0,105
	Deceased	9,18	8,95	1,05	7,8	12	
Hgb (g/dl)	Alive	11,68	11	2,33	7	17,3	0,103
	Deceased	10,48	10,35	1,31	8,7	12,7	
Albumin (g/dl)	Alive	3,08	3,1	0,62	1,4	4,19	0,163
	Deceased	2,88	2,7	0,51	2,1	4,08	
Procalcitonin (ng/ml)	Alive	3,77	0,295	6,79	0,2	20	0,205
	Deceased	21,3	3,2	32	0,16	100	

Discussion

In a study conducted by Osmonov et al. in our country, in a retrospective study of CIED-related IEs that developed within 31 years in a single center, 23 (0.38%) of 5287 patients with CIED were reported to develop IE [6]. When Aksoy et al. examined the main differences in the characteristics and management of IE between both sexes in their 11-year follow-up study of patients with endocarditis, response to antibiotic therapy, need for surgical treatment, surgical intervention rate, and the overall in-hospital mortality were similar in both genders [7-9]. In our study, the ratio of female and male patients was equal. However, among surviving patients, women were more common (21 (87.5%), and among those who died, men were more common (9 (37.5%)). In the study by Bloom et al., the risk factors most commonly associated with endocarditis were diabetes mellitus and chronic kidney disease [10,11]. In our study, HT was detected in 13 (86%) patients, chronic renal failure in 9 patients (47%), and DM in 8 patients (72%), in order of frequency in surviving patients. Of the patients who died, 10 (52%) had CRF, 3 (27%) had DM, 2 (66%) had HT and COPD.

In the study by Massoure et al., 51-80% of 155 patients had a fever, and 68-92% had bacteremia [12]. In a multicenter study by Sohail et al., in 177 patients, fever and chills were found in 55.3%, vegetation in 67.6%, and positive blood cultures in 34.5% [13]. In our study, the most common symptoms in surviving patients were, respectively, fever in 26 (78%), fatigue in 19 (76%) patients, respiratory distress in 11 (61%) patients. Among those who died, respiratory distress was present in 7 (38%), fever in 7 (21%), and fatigue in 6 (24%) patients.

In the study conducted by Sohail et al., blood cultures were positive in 77%, vegetation in 67.6%, and positive blood cultures consistent with endocarditis in 34.5% of patients who were thought to have cardiac device-related infection [13]. Consistent with other studies, blood culture positivity was found to be 54% in our study. In these patients with the preliminary diagnosis of fever of unknown origin, antibiotics were started before blood cultures were taken.

In the study by Rundstrom et al., CRP elevation was observed in 73% to 100% of patients with pacemaker endocarditis and in 34% to 81.8% of leukocytosis cases [14]. In our study, 16 (70%) of the surviving patients and 7 (30%) of the deceased patients had serum leukocytosis. C-reactive protein (CRP) was found to be higher than 20mg/dl in 27 (80%) of the survivors and 7 (20%) of the patients who died. Staphylococci and especially coagulase-negative Staphylococci account for 60-80% of cases. Polymicrobial infection, Corynebacterium spp., Propionibacterium acnes, Gram-negative bacilli and Candida spp. are rarely identified as pathogens in CIED infection [15]. In our study, the most frequently isolated pathogens were Staphylococcus aureus (n=11) 42% and Streptococcus spp (n=6) 23%, Enterococcus faecium (n=4) 1%, Citrobacter spp (n=2) 7.6%, Diphtheroid spp (n=1) 3.8%, Acinetobacter baumannii (n=1) 3%, Brucella mitis (n=1) 3%.

The role of echocardiography is very important in the diagnosis of cardiac device-related IE. Echocardiography helps detect electrode vegetation and tricuspid valve involvement and quantify tricuspid regurgitation [14]. In the multicenter study by Athan et al., fever, vegetation and positive blood culture

were high (>80%). In this study, the sensitivity of TTE was low, vegetations were visualized in 30.4% of the patients [16]. In our study, consistent with other studies, vegetation on the lead was observed on ECHO and/or TTE in 13 (27%) patients.

In the majority of patients with cardiac device-associated IE, device removal is required with prolonged administration of antibiotics [14]. In most patients, the lead can be removed percutaneously without the need for surgical intervention. However, if the cardiac device was placed several years ago, percutaneous electrode removal becomes difficult. In such cases, surgical intervention is recommended in the presence of severe tricuspid valve endocarditis and in patients with large vegetations [17]. In our study, 29 (60%) patients underwent surgical treatment.

The 30-day mortality rate for CIED infection is 5-8%. Female gender is a high-risk factor for endocarditis. Successfully treated patients have the same prognosis as patients who have never been infected [18]. In our study, 21 women survived (87%), 3 died (17%), and 15 (62%) male patients survived, 9 died (38%).

Conclusion

In our country, studies and the number of cases of endocarditis related to CIEDs are limited. Although endocarditis from CIEDs is a rare complication of cardiac device implantation, its morbidity and mortality remain high.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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